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Nontargeted Metabolomic Analysis in Kidney Cortex and Medulla of a 5/6 Nephrectomy Rat Model Using UPLC/QTOF-MS

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Objectives : Metabolomics profiling in chronic kidney disease (CKD) has the potential to identify novel biomarkers and provide insight into disease pathogenesis. However, region-specific metabolite signatures in the kidney remain unclear as CKD risk factors for ESRD. Here, we use ultra-high performance liquid chromatograph with quadrupole time-of-flight mass spectrometry (UPLC/QTOF-MS) to analyze cortex and medulla-specific metabolites in sham and 5/6 nephrectomy (5/6 Nx) rats.
Methods : In the 5/6 Nx rat model, we isolated the kidney cortex and medulla with high purity based on their anatomical characteristics at 0, 2, 4, and 8 weeks' post-operation. Metabolic profiling using ultra-high performance liquid chromatography coupled with quadrupole time-of-flight mass spectrometry (UPLC/QTOF-MS) revealed distinct metabolic alterations in the cortex and medulla associated with kidney dysfunction and fibrosis progression.
Results : Principal component analysis (PCA) revealed distinct separations between the sham and 5/6 Nx groups in both positive and negative modes. In the 5/6 Nx model, metabolic changes over time were more pronounced in the cortex than in the medulla. Notably, the uremic toxins indoxyl sulfate, hippuric acid, and trimethylamine-N-oxide (TMAO) began increasing in both regions from 2 weeks post-nephrectomy, with greater elevation in the cortex. Indoxyl sulfate exhibited an early peak after nephrectomy, followed by a gradual increase, suggesting a dynamic interplay between skeletal muscle loss and kidney function deterioration. Meanwhile, hippuric acid and TMAO showed a continuous rise through disease progression, linking these metabolic alterations to impaired glomerular filtration and the accumulation of uremic toxins
Conclusions : A metabolomics-based approach reveals that indoxyl sulfate in an early indicator of potential fibrosis in both the cortex and medulla, compared to TMAO and hippuric acid. Thus, inhibiting indoxyl sulfate may offer a promising strategy to prevent uremic toxin-related kidney fibrosis.